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NEWS 3 SEP 09 CA/CAPLUS records now contain indexing from 1907 to the
present
NEWS 4 AUG 05 New pricing for EUROPATFULL and PCTFULL effective
August 1, 2003
NEWS 5 AUG 13 Field Availability (/FA) field enhanced in BEILSTEIN
NEWS 6 AUG 18 Data available for download as a PDF in RDISCLOSURE
NEWS 7 AUG 18 Simultaneous left and right truncation added to PASCAL
NEWS 8 AUG 18 FROSTI and KOSMET enhanced with Simultaneous Left and Right
Truncation
NEWS 9 AUG 18 Simultaneous left and right truncation added to ANABSTR
NEWS 10 SEP 22 DIPPR file reloaded
NEWS 11 SEP 25 INPADOC: Legal Status data to be reloaded
NEWS 12 SEP 29 DISSABS now available on STN
NEWS 13 OCT 10 PCTFULL: Two new display fields added
NEWS 14 OCT 21 BIOSIS file reloaded and enhanced
NEWS 15 OCT 28 BIOSIS file segment of TOXCENTER reloaded and enhanced

NEWS EXPRESS NOVEMBER 14 CURRENT WINDOWS VERSION IS V6.01c, CURRENT
MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
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FILE 'HOME' ENTERED AT 12:49:06 ON 21 NOV 2003

=> file medline, uspatful, wpids, jicst, fsta, hcaplus		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	1.68	1.68

FILE 'MEDLINE' ENTERED AT 12:53:40 ON 21 NOV 2003

FILE 'USPATFULL' ENTERED AT 12:53:40 ON 21 NOV 2003
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=> s IgE fragment

L1 898 IGE FRAGMENT

=> s IgE

L2 59183 IGE

=> s clostridium botulinum

L3 8710 CLOSTRIDIUM BOTULINUM

=> s neisseria gonorrhoeae

L4 406 NEISSERIA GONORRHEAE

=> s fusion protein or hybrid protein

L5 73853 FUSION PROTEIN OR HYBRID PROTEIN

=> s mastocytes

L6 719 MASTOCYTES

=> s basophils

L7 14279 BASOPHILS

=> s tetanus toxin

L8 6169 TETANUS TOXIN

=> s 12 and 15

L9 5949 L2 AND L5

=> s 19 and 16

L10 5 L9 AND L6

=> d l10 ti abs ibib tot

L10 ANSWER 1 OF 5 USPATFULL on STN

TI Cloning and sequencing of the allergen Dac g5 of Dactylis glomerata pollen, its preparation and its use

AB A purified nucleic acid molecule comprising a nucleotide sequence coding for allergen Dac g5 having amino acid sequence SEQ ID NO. 2, a derivative or a fragment thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:213243 USPATFULL

TITLE: Cloning and sequencing of the allergen Dac g5 of Dactylis glomerata pollen, its preparation and its use

INVENTOR(S): Van Ree, Ronald, Amsterdam, NETHERLANDS
Van Oort, Erica, Vleuten, NETHERLANDS
Bonneau, Caroline, Rouen, FRANCE
Faye, Loic, Saint-Jacques-sur-Darnetal, FRANCE

PATENT ASSIGNEE(S): Gomord, Veronique, Rouen, FRANCE
Seita Groupe Altadis, Paris Cedex, FRANCE (non-U.S.
corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003147880	A1	20030807
APPLICATION INFO.:	US 2002-303426	A1	20021125 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2001-FR1666, filed on 29 May 2001, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	FR 2000-6857	20000529
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	SCHNADER HARRISON SEGAL & LEWIS, LLP, 1600 MARKET STREET, SUITE 3600, PHILADELPHIA, PA, 19103	
NUMBER OF CLAIMS:	20	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	2 Drawing Page(s)	
LINE COUNT:	829	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		

L10 ANSWER 2 OF 5 USPATFULL on STN

TI Factors participating in degranulation of mast cells, dnas encoding the
same, method of screening of these factors and the inhibitors

AB The present invention provides a novel protein that regulates
degranulation of mast cells (degranulation regulator), a gene encoding
it, a protein (conjugate factor) that interacts with the regulator, a
gene encoding it, a screening method of an inhibitor of the
degranulation, which uses this degranulation regulator and the conjugate
factor, an inhibitor obtained by the screening method and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:207275 USPATFULL

TITLE: Factors participating in degranulation of mast cells,
dnas encoding the same, method of screening of these
factors and the inhibitors

INVENTOR(S): Yamada, Tsuyoshi, Chiba, JAPAN
Ido, Motoharu, Shiga, JAPAN

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003143633	A1	20030731
APPLICATION INFO.:	US 2002-258107	A1	20021219 (10)
	WO 2001-JP3268		20010416

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2000-118408	20000419
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LEYDIG VOIT & MAYER, LTD, TWO PRUDENTIAL PLAZA, SUITE 4900, 180 NORTH STETSON AVENUE, CHICAGO, IL, 60601-6780	
NUMBER OF CLAIMS:	41	
EXEMPLARY CLAIM:	1	
LINE COUNT:	2008	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		

L10 ANSWER 3 OF 5 USPATFULL on STN

TI Hybrid protein for inhibiting the degranulation of
mastocytes and the use thereof

AB A hybrid protein contains a protein that binds to a

receptor of mastocytes and basophils and is endocytosed by them. The protein can be IgE; IgE fragment; IgE Fc fragment; antibody against IgE receptor of mastocytes and basophils; fragment of the antibody against the IgE receptor of mastocytes and basophils; antibody against mastocyte specific potassium channel; and mast cell degranulating peptide. The hybrid protein also contains a protease cleaving proteins of the secretion process of the mastocytes and basophils so as to inhibit the secretion process without killing the mastocytes and basophils. The protease can be light chain Clostridium botulinum toxin; proteolytically active fragment of the light chain of a Clostridium botulinum toxin containing an amino acid sequence His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His wherein Xaa is an amino acid; light chain of the tetanus toxin; proteolytically active fragment of the light chain of the tetanus toxin containing His-Asp-Leu-Ile-His-Val-Leu-His; IgA protease of Neisseria gonorrhoeae; and proteolytic domain of the IgA protease of Neisseria gonorrhoeae.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:86306 USPATFULL

TITLE: Hybrid protein for inhibiting the degranulation of mastocytes and the use thereof

INVENTOR(S): Bigalke, Hans, Hannover, GERMANY, FEDERAL REPUBLIC OF Frevert, Jurgen, Berlin, GERMANY, FEDERAL REPUBLIC OF

PATENT ASSIGNEE(S): BioteCon Gesellschaft fur biotechnologische Entwicklung und consulting mbH, Berlin, DE, 10589 (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003059912	A1	20030327
APPLICATION INFO.:	US 2002-64903	A1	20020827 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-700540, filed on 19 Jan 2001, PENDING A 371 of International Ser. No. WO 1999-EP3272, filed on 12 May 1999, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1998-19821285	19980513
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	GUDRUN E. HUCKETT, LONSSTR. 53, WUPPERTAL, 42289	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
LINE COUNT:	576	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2003 ACS on STN

TI Inhibiting the degranulation in mastocytes using a hybrid protein comprising a receptor-binding protein fused to a protease cleaving a protein of the secretion process

AB A hybrid protein is provided contg. a protein that binds to a receptor of mastocytes and basophils and is endocytosed by them. The protein can be IgE, IgE fragment, IgE Fc fragment, antibody against the IgE receptor of mastocytes and basophils, a fragment of the antibody against the IgE receptor of mastocytes and basophils, an antibody against mastocyte-specific potassium channel, or mast cell degranulating peptide. The hybrid protein also contains a protease which cleaves proteins of the secretion process of the mastocytes and basophils so as to inhibit the secretion process without killing the mastocytes and basophils. The protease can be the light chain of Clostridium botulinum toxin or its proteolytic

fragments contg. a His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His sequence, the light chain of the tetanus toxin or proteolytically active fragment of the light chain contg. His-Asp-Leu-Ile-His-Val-Leu-His, or an IgA protease of *Neisseria gonorrhoeae* and its proteolytic domain. Thus, a **hybrid protein** comprising IgE fused to the light chain of either *Clostridium botulinum* toxin or tetanus toxin prevents allergic shock caused by dying **mastocytes**.

ACCESSION NUMBER: 2003:241912 HCAPLUS
DOCUMENT NUMBER: 138:265639
TITLE: Inhibiting the degranulation in **mastocytes** using a **hybrid protein** comprising a receptor-binding protein fused to a protease cleaving a protein of the secretion process
INVENTOR(S): Bigalke, Hans; Frevert, Jurgen
PATENT ASSIGNEE(S): Biotecon Gesellschaft Fur Biotechnologische Entwicklung Und Consulting Mbh, Germany
SOURCE: U.S. Pat. Appl. Publ., 7 pp., Cont.-in-part of U.S. Ser. No. 700,540.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003059912	A1	20030327	US 2002-64903	20020827
WO 9958571	A2	19991118	WO 1999-EP3272	19990512
WO 9958571	A3	20000203		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
DE 1998-19821285 A 19980513
WO 1999-EP3272 W 19990512
US 2001-700540 A2 20010119

L10 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2003 ACS on STN

TI **Hybrid protein** for inhibiting the degranulation of **mastocytes** and the use thereof

AB The invention relates to a **hybrid protein** comprising or comprised of (i) a known protein which binds to **mastocytes** and/or basophils in a known manner and/or is absorbed thereby, and of (ii) a protease which splits one or more proteins of the secretory app. of the **mastocytes** and/or basophils. The examples discuss the synthesis of these hybrid proteins using expression vectors expressed in *E. coli*.

ACCESSION NUMBER: 1999:736768 HCAPLUS
DOCUMENT NUMBER: 131:332099
TITLE: **Hybrid protein** for inhibiting the degranulation of **mastocytes** and the use thereof
INVENTOR(S): Bigalke, Hans; Frevert, Jurgen
PATENT ASSIGNEE(S): Biotecon Gesellschaft fur Biotechnologische Entwicklung und Consulting m.b.H, Germany
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958571	A2	19991118	WO 1999-EP3272	19990512
WO 9958571	A3	20000203		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2331274	AA	19991118	CA 1999-2331274	19990512
AU 9942605	A1	19991129	AU 1999-42605	19990512
AU 755513	B2	20021212		
BR 9910359	A	20010109	BR 1999-10359	19990512
EP 1084146	A2	20010321	EP 1999-950347	19990512
EP 1084146	B1	20021113		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002514659	T2	20020521	JP 2000-548373	19990512
AT 227739	E	20021115	AT 1999-950347	19990512
ES 2187200	T3	20030516	ES 1999-950347	19990512
RU 2214420	C2	20031020	RU 2000-131217	19990512
NO 2000005637	A	20001108	NO 2000-5637	20001108
HK 1036994	A1	20030221	HK 2001-106685	20010921
US 2003059912	A1	20030327	US 2002-64903	20020827
PRIORITY APPLN. INFO.:			DE 1998-19821285 A	19980513
			WO 1999-EP3272 W	19990512
			US 2001-700540 A2	20010119

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FILE 'MEDLINE, USPATFULL, WPIDS, JICST-EPLUS, FSTA, HCAPLUS' ENTERED AT 12:53:40 ON 21 NOV 2003

L1 898 S IGE FRAGMENT
L2 59183 S IGE
L3 8710 S CLOSTRIDIUM BOTULINUM
L4 406 S NEISSERIA GONORRHEAE
L5 73853 S FUSION PROTEIN OR HYBRID PROTEIN
L6 719 S MASTOCYTES
L7 14279 S BASOPHILS
L8 6169 S TETANUS TOXIN
L9 5949 S L2 AND L5
L10 5 S L9 AND L6

=> s l3 and type A

4 FILES SEARCHED...

L11 1541 L3 AND TYPE A

=> s IgA protease

L12 383 IGA PROTEASE

=> s l2 and toxin

L13 4861 L2 AND TOXIN

=> s l13 and transport

L14 1816 L13 AND TRANSPORT

=> s l14 and l6
L15 1 L14 AND L6

=> d l15 ti abs ibib tot

L15 ANSWER 1 OF 1 USPATFULL on STN

TI Hybrid protein for inhibiting the degranulation of mastocytes and the use thereof

AB A hybrid protein contains a protein that binds to a receptor of mastocytes and basophils and is endocytosed by them. The protein can be IgE; IgE fragment; IgE Fc fragment; antibody against IgE receptor of mastocytes and basophils; fragment of the antibody against the IgE receptor of mastocytes and basophils; antibody against mastocyte specific potassium channel; and mast cell degranulating peptide. The hybrid protein also contains a protease cleaving proteins of the secretion process of the mastocytes and basophils so as to inhibit the secretion process without killing the mastocytes and basophils. The protease can be light chain Clostridium botulinum toxin; proteolytically active fragment of the light chain of a Clostridium botulinum toxin containing an amino acid sequence His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His wherein Xaa is an amino acid; light chain of the tetanus toxin; proteolytically active fragment of the light chain of the tetanus toxin containing His-Asp-Leu-Ile-His-Val-Leu-His; IgA protease of Neisseria gonorrhoeae; and proteolytic domain of the IgA protease of Neisseria gonorrhoeae.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:86306 USPATFULL

TITLE: Hybrid protein for inhibiting the degranulation of mastocytes and the use thereof

INVENTOR(S): Bigalke, Hans, Hannover, GERMANY, FEDERAL REPUBLIC OF Frevert, Jurgen, Berlin, GERMANY, FEDERAL REPUBLIC OF

PATENT ASSIGNEE(S): BioteCon Gesellschaft fur biotechnologische Entwicklung und consulting mbH, Berlin, DE, 10589 (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003059912	A1	20030327
APPLICATION INFO.:	US 2002-64903	A1	20020827 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-700540, filed on 19 Jan 2001, PENDING A 371 of International Ser. No. WO 1999-EP3272, filed on 12 May 1999, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1998-19821285	19980513
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	GUDRUN E. HUCKETT, LONSSTR. 53, WUPPERTAL, 42289	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
LINE COUNT:	576	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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(FILE 'HOME' ENTERED AT 12:49:06 ON 21 NOV 2003)

FILE 'MEDLINE, USPATFULL, WPIDS, JICST-EPLUS, FSTA, HCAPLUS' ENTERED AT 12:53:40 ON 21 NOV 2003

L1 898 S IGE FRAGMENT

L2 59183 S IGE
 L3 8710 S CLOSTRIDIUM BOTULINUM
 L4 406 S NEISSERIA GONORRHEAE
 L5 73853 S FUSION PROTEIN OR HYBRID PROTEIN
 L6 719 S MASTOCYTES
 L7 14279 S BASOPHILS
 L8 6169 S TETANUS TOXIN
 L9 5949 S L2 AND L5
 L10 5 S L9 AND L6
 L11 1541 S L3 AND TYPE A
 L12 383 S IGA PROTEASE
 L13 4861 S L2 AND TOXIN
 L14 1816 S L13 AND TRANSPORT
 L15 1 S L14 AND L6

=> s l14 and l7

L16 406 L14 AND L7

=> s l16 and l1

L17 6 L16 AND L1

=> d l17 ti abs ibib tot

L17 ANSWER 1 OF 6 USPATFULL on STN

TI Anti-IgE antibodies

AB The present invention relates to a method for adjusting the affinity of a polypeptide to a target molecule by a combination of steps, including: (1) the identification of aspartyl residues which are prone to isomerization; (2) the substitution of alternative residues and screening the resulting mutants for affinity against the target molecule. In a preferred embodiment, the method of substituting residues is affinity maturation with phage display (AMPD). In a further preferred embodiment the polypeptide is an antibody and the target molecule is an antigen. In a further preferred embodiment, the antibody is anti-IgE and the target molecule is IgE. In another embodiment, the invention relates to an anti-IgE antibody having improved affinity to IgE.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:214601 USPATFULL

TITLE: Anti-IgE antibodies

INVENTOR(S): Lowman, Henry B., El Granada, CA, UNITED STATES
 Presta, Leonard G., San Francisco, CA, UNITED STATES
 Jardieu, Paula M., San Mateo, CA, UNITED STATES
 Lowe, John, Daly City, CA, UNITED STATES
 PATENT ASSIGNEE(S): Genentech, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003149244	A1	20030807
APPLICATION INFO.:	US 2002-113996	A1	20020401 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2001-920171, filed on 1 Aug 2001, PENDING Continuation of Ser. No. US 1999-296005, filed on 21 Apr 1999, GRANTED, Pat. No. US 6290957		
	Continuation of Ser. No. US 1997-887352, filed on 2 Jul 1997, GRANTED, Pat. No. US 5994511		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	GENENTECH, INC., 1 DNA WAY, SOUTH SAN FRANCISCO, CA, 94080.		
NUMBER OF CLAIMS:	31		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	19 Drawing Page(s)		
LINE COUNT:	5839		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 2 OF 6 USPATFULL on STN

TI Hybrid protein for inhibiting the degranulation of mastocytes and the use thereof

AB A hybrid protein contains a protein that binds to a receptor of mastocytes and **basophils** and is endocytosed by them. The protein can be **IgE**; **IgE fragment**; **IgE Fc fragment**; antibody against **IgE** receptor of mastocytes and **basophils**; fragment of the antibody against the **IgE** receptor of mastocytes and **basophils**; antibody against mastocyte specific potassium channel; and mast cell degranulating peptide. The hybrid protein also contains a protease cleaving proteins of the secretion process of the mastocytes and **basophils** so as to inhibit the secretion process without killing the mastocytes and **basophils**. The protease can be light chain Clostridium botulinum toxin; proteolytically active fragment of the light chain of a Clostridium botulinum toxin containing an amino acid sequence His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His wherein Xaa is an amino acid; light chain of the tetanus toxin; proteolytically active fragment of the light chain of the tetanus toxin containing His-Asp-Leu-Ile-His-Val-Leu-His; IgA protease of Neisseria gonorrhoeae; and proteolytic domain of the IgA protease of Neisseria gonorrhoeae.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:86306 USPATFULL

TITLE: Hybrid protein for inhibiting the degranulation of mastocytes and the use thereof

INVENTOR(S): Bigalke, Hans, Hannover, GERMANY, FEDERAL REPUBLIC OF Frevert, Jurgen, Berlin, GERMANY, FEDERAL REPUBLIC OF

PATENT ASSIGNEE(S): BioteCon Gesellschaft fur biotechnologische Entwicklung und consulting mbH, Berlin, DE, 10589 (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003059912	A1	20030327
APPLICATION INFO.:	US 2002-64903	A1	20020827 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-700540, filed on 19 Jan 2001, PENDING A 371 of International Ser. No. WO 1999-EP3272, filed on 12 May 1999, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1998-19821285	19980513
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	GUDRUN E. HUCKETT, LONSSTR. 53, WUPPERTAL, 42289	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
LINE COUNT:	576	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 3 OF 6 USPATFULL on STN

TI Anti-IgE antibodies

AB The present invention relates to a method for adjusting the affinity of a polypeptide to a target molecule by a combination of steps, including: (1) the identification of aspartyl residues which are prone to isomerization; (2) the substitution of alternative residues and screening the resulting mutants for affinity against the target molecule. In a preferred embodiment, the method of substituting residues is affinity maturation with phage display (AMPD). In a further preferred embodiment the polypeptide is an antibody and the target molecule is an antigen. In a further preferred embodiment, the antibody is anti-

IgE and the target molecule is IgE. In another embodiment, the invention relates to an anti-IgE antibody having improved affinity to IgE.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:105676 USPATFULL
TITLE: Anti-IgE antibodies
INVENTOR(S): Lowman, Henry B., El Granada, CA, UNITED STATES
Presta, Leonard G., San Francisco, CA, UNITED STATES
Jardieu, Paula M., San Mateo, CA, UNITED STATES
Lowe, John, Daly City, CA, UNITED STATES
PATENT ASSIGNEE(S): Genentech, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002054878	A1	20020509
APPLICATION INFO.:	US 2001-920171	A1	20010801 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1999-296005, filed on 21 Apr 1999, GRANTED, Pat. No. US 6290957 Continuation of Ser. No. US 1997-887352, filed on 2 Jul 1997, GRANTED, Pat. No. US 5994511		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	GENENTECH, INC., 1 DNA WAY, SOUTH SAN FRANCISCO, CA, 94080		
NUMBER OF CLAIMS:	31		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	19 Drawing Page(s)		
LINE COUNT:	5846		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 4 OF 6 USPATFULL on STN

TI Anti-IgE antibodies and method of improving polypeptides
AB The present invention relates to a method for adjusting the affinity of a polypeptide to a target molecule by a combination of steps, including: (1) the identification of aspartyl residues which are prone to isomerization; (2) the substitution of alternative residues and screening the resulting mutants for affinity against the target molecule. In a preferred embodiment, the method of substituting residues is affinity maturation with phage display (AMPD). In a further preferred embodiment the polypeptide is an antibody and the target molecule is an antigen. In a further preferred embodiment, the antibody is anti-IgE and the target molecule is IgE. In another embodiment, the invention relates to an anti-IgE antibody having improved affinity to IgE.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2001:157795 USPATFULL
TITLE: Anti-IgE antibodies and method of improving polypeptides
INVENTOR(S): Lowman, Henry B., 400 San Juan Ave., El Granada, CA, United States 94018
Presta, Leonard G., 1900 Gough St. #206, San Francisco, CA, United States 94109
Jardieu, Paula M., 33 Hayward Ave. #110, San Mateo, CA, United States 94401-4319
Lowe, John, 396 Michelle La., Daly City, CA, United States 94080

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6290957	B1	20010918
APPLICATION INFO.:	US 1999-296005		19990421 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1997-887352, filed on 2 Jul		

1997, now patented, Pat. No: US 5994511
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Saunders, David
LEGAL REPRESENTATIVE: Svoboda, Craig G.
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 21 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT: 4910
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 5 OF 6 USPATFULL on STN

TI Anti-IgE antibodies and method of improving polypeptides
AB The present invention relates to a method for adjusting the affinity of a polypeptide to a target molecule by a combination of steps, including: (1) the identification of aspartyl residues which are prone to isomerization; (2) the substitution of alternative residues and screening the resulting mutants for affinity against the target molecule. In a preferred embodiment, the method of substituting residues is affinity maturation with phage display (AMPD). In a further preferred embodiment the polypeptide is an antibody and the target molecule is an antigen. In a further preferred embodiment, the antibody is anti-IgE and the target molecule is IgE. In another embodiment, the invention relates to an anti-IgE antibody having improved affinity to IgE.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2001:4887 USPATFULL
TITLE: Anti-IgE antibodies and method of improving polypeptides
INVENTOR(S): Lowman, Henry B., El Granada, CA, United States
Presta, Leonard G., San Francisco, CA, United States
Jardieu, Paula M., San Mateo, CA, United States
Lowe, John, Daly City, CA, United States
PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6172213	B1	20010109
APPLICATION INFO.:	US 1998-109207		19980630 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-51554P	19970702 (60)

DOCUMENT TYPE: Patent
FILE SEGMENT: Granted
PRIMARY EXAMINER: Chan, Christina Y.
ASSISTANT EXAMINER: Ewoldt, Gerald R.
LEGAL REPRESENTATIVE: Svoboda, Craig G.
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 23 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT: 4829
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 6 OF 6 USPATFULL on STN

TI Anti-IgE antibodies and methods of improving polypeptides
AB The present invention relates to a method for adjusting the affinity of a polypeptide to a target molecule by a combination of steps, including: (1) the identification of aspartyl residues which are prone to isomerization; (2) the substitution of alternative residues and screening the resulting mutants for affinity against the target molecule. In a preferred embodiment, the method of substituting residues

is affinity maturation with phage display (AMPD). In a further preferred embodiment the polypeptide is an antibody and the target molecule is an antigen. In a further preferred embodiment, the antibody is anti-IgE and the target molecule is IgE. In another embodiment, the invention relates to an anti-IgE antibody having improved affinity to IgE.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 1999:155894 USPATFULL
 TITLE: Anti-IgE antibodies and methods of improving polypeptides
 INVENTOR(S): Lowman, Henry B., El Granada, CA, United States
 Presta, Leonard G., San Francisco, CA, United States
 Jardieu, Paula M., San Mateo, CA, United States
 Lowe, John, Daly City, CA, United States
 PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, United States
 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5994511		19991130
APPLICATION INFO.:	US 1997-887352		19970702 (8)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Saunders, David		
LEGAL REPRESENTATIVE:	Svoboda, Craig G.		
NUMBER OF CLAIMS:	11		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	21 Drawing Figure(s); 19 Drawing Page(s)		
LINE COUNT:	5816		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> s degranulation
 L18 15947 DEGRANULATION

=> d his

(FILE 'HOME' ENTERED AT 12:49:06 ON 21 NOV 2003)

FILE 'MEDLINE, USPATFULL, WPIDS, JICST-EPLUS, FSTA, HCAPLUS' ENTERED AT 12:53:40 ON 21 NOV 2003

L1 898 S IGE FRAGMENT
 L2 59183 S IGE
 L3 8710 S CLOSTRIDIUM BOTULINUM
 L4 406 S NEISSERIA GONORRHEAE
 L5 73853 S FUSION PROTEIN OR HYBRID PROTEIN
 L6 719 S MASTOCYTES
 L7 14279 S BASOPHILS
 L8 6169 S TETANUS TOXIN
 L9 5949 S L2 AND L5
 L10 5 S L9 AND L6
 L11 1541 S L3 AND TYPE A
 L12 383 S IGA PROTEASE
 L13 4861 S L2 AND TOXIN
 L14 1816 S L13 AND TRANSPORT
 L15 1 S L14 AND L6
 L16 406 S L14 AND L7
 L17 6 S L16 AND L1
 L18 15947 S DEGRANULATION

=> s l18 and prevention
 L19 1464 L18 AND PREVENTION

=> s 118 and 16
L20 147 L18 AND L6

=> s 118 and 17
L21 1780 L18 AND L7

=> s 120 and inhibition
L22 40 L20 AND INHIBITION

=> s 119 and inhibition
L23 1032 L19 AND INHIBITION

=> s 122 and 123
L24 13 L22 AND L23

=> d 124 ti abs ibib tot

L24 ANSWER 1 OF 13 MEDLINE on STN

TI [Allergic risk of aprotinin].

Le risque allergique de l'aprotinine.

AB OBJECTIVE: To analyse the risk of anaphylactic reaction with the administration of aprotinin, either by i.v. route or as a biological sealant application and to propose updated guidelines in accordance with current data of the literature. DATA SOURCES: Search in the Medline data base of articles in French, English and German, published since 1960, using following key words: aprotinin, allergy, anaphylaxis. STUDY SELECTION: All categories of articles on this topic have been selected. DATA EXTRACTION: Articles have been analysed for history, incidence and mechanisms of anaphylactic reactions, symptomatology, factors of risk, diagnosis and precautions of use. DATA SYNTHESIS: Aprotinin is widely used for decreasing preoperative bleeding, especially in cardiac and orthopaedic surgery. This heterologue protein can cause anaphylactic reactions in 0.5 to 5.8% of patients, depending of the inclusion criteria. They are mediated by IgG and IgE antibodies. Aprotinin has also a direct, non specific, histaminoliberation effect. The clinical presentation includes various degrees of severity, up to cardiac arrest. Documented factors of risk are a previous parotinin administration, 15 days to 6 months before, and intolerance to beef meat, white of egg, cheese and milk. The immediate biological diagnosis is obtained on assessing the degranulation of basophiles (histamine) and mastocytes (tryptase), as well as the concentration of anti-aprotinin antibodies (RAST IgE), with a test of inhibition. The secondary assessment, six weeks later, includes prick-tests and intradermoreactions if the former are negative. The mean precaution consists to search factors of risk at preanaesthetic assessment. The predictive value of systematic prick-tests has not yet been validated. Anti H1 and anti H2 premedication is inefficient. A test dose can trigger a severe reaction. CONCLUSION: Considering a significant anaphylactic risk, aprotinin administration becomes only licit after a careful evaluation of the benefit-risk ratio.

ACCESSION NUMBER: 2000194364 MEDLINE

DOCUMENT NUMBER: 20194364 PubMed ID: 10730171

TITLE: [Allergic risk of aprotinin].

Le risque allergique de l'aprotinine.

AUTHOR: Laxenaire M C; Dewachter P; Pecquet C

CORPORATE SOURCE: Departement d'anesthesie-reanimation, hopital central, Nancy.

SOURCE: ANNALES FRANCAISES D ANESTHESIE ET DE REANIMATION, (2000 Feb) 19 (2) 96-104. Ref: 49

Journal code: 8213275. ISSN: 0750-7658.

PUB. COUNTRY: France

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000424

L24 ANSWER 2 OF 13 MEDLINE on STN

TI [Cromoglycic acid (disodium cromoglycate) and inhibitors of mast cell degranulation].

Acide cromoglicique (cromoglycate disodique) et inhibiteurs de la degranulation des mastocytes.

AB Cromoglycic acid (disodium cromoglycate) is a diacromone derived from khelline whose chief action in asthma is preventive, through inhibition of mastocyte degranulation. Since its digestive absorption is poor, it is given locally as a pulverulent aerosol. Cromoglycic acid is also used successfully in certain forms of ocular and nasal allergy. An oral preparation of cromoglycic acid is beginning to be used in food allergy and certain rectocolites. Trials are ongoing with several other substances, which have comparable properties and are active orally.

ACCESSION NUMBER: 84172265 MEDLINE

DOCUMENT NUMBER: 84172265 PubMed ID: 6324375

TITLE: [Cromoglycic acid (disodium cromoglycate) and inhibitors of mast cell degranulation].

Acide cromoglicique (cromoglycate disodique) et inhibiteurs de la degranulation des mastocytes.

AUTHOR: Advenier C; Ruff F

SOURCE: SEMAINE DES HOPITAUX, (1984 Feb 23) 60 (9) 659-64. Ref: 68
Journal code: 9410059.

PUB. COUNTRY: France

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LANGUAGE: French

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198405

ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19840510

L24 ANSWER 3 OF 13 USPATFULL on STN

TI 1-alkyl or 1-cycloalkyltriazolo[4,3-a]quinazolin-5-ones as phosphodiesterase inhibitors

AB The invention relates to compounds of formula (I), ##STR1##

in which R.sup.1, R.sup.2 and R.sup.3 are as defined in the description, their use as medicaments, the process for their preparation and their use for the treatment of pathologies in which therapy by a PDE4 inhibitor is relevant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:100149 USPATFULL

TITLE: 1-alkyl or 1-cycloalkyltriazolo[4,3-a]quinazolin-5-ones as phosphodiesterase inhibitors

INVENTOR(S): Guadilliere, Bernard, Nanterre, FRANCE
Lavalette, Remi, Longjumeau, FRANCE

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003069260	A1	20030410
APPLICATION INFO.:	US 2002-211134	A1	20020802 (10)

NUMBER	DATE
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PRIORITY INFORMATION: EP 2001-402166 20010813
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PFIZER INC., PATENT DEPARTMENT, MS8260-1611, EASTERN
POINT ROAD, GROTON, CT, 06340
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
LINE COUNT: 1081
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 4 OF 13 USPATFULL on STN

TI Immunogenic compounds with in particular an anti-cytokine effect,
preparation process, pharmaceutical compositions and kits containing
them
AB Cytokines, which are biologically inactive in humans but remain
immunogenic, are used in pharmaceutical compositions to promote a
neutralizing immune response against native cytokines when administrated
to a subject in need thereof to treat homeostatic conditions and
disorders associated with an overproduction of cytokines.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:246370 USPATFULL
TITLE: Immunogenic compounds with in particular an
anti-cytokine effect, preparation process,
pharmaceutical compositions and kits containing them
INVENTOR(S): Zagury, Daniel, Paris, FRANCE
Zagury, Jean-Fran.cedilla.ois, Paris, FRANCE
Bizzini, Bernard, Le Mesnil-Saint-Denis, FRANCE
PATENT ASSIGNEE(S): Neovacs, Paris, FRANCE (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6455045	B1	20020924
APPLICATION INFO.:	US 1999-317993		19990525 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1994-167867, filed on 27 Jun 1994, now patented, Pat. No. US 6093405		

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1991-7399	19910617
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Scheiner, Laurie	
ASSISTANT EXAMINER:	Parkin, Jeffrey S.	
LEGAL REPRESENTATIVE:	Browdy and Neimark	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)	
LINE COUNT:	1222	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 5 OF 13 USPATFULL on STN

TI Aerosolized anti-infectives, anti-inflammatories, and decongestants for
the treatment of sinusitis
AB Pharmaceutical compositions are described that comprise one or more
active ingredients selected from the group consisting of an
anti-infective agent, anti-inflammatory agent, anti-mucolytic agent,
antihistamine, an antiseptic, and antibiotic combinations or
combinations of others of these classes of ingredients, and particularly
to compositions formulated as a solution or suspension in a unit dose
for aerosol administration to treat chronic sinusitis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:119301 USPATFULL

TITLE: Aerosolized anti-infectives, anti-inflammatories, and
decongestants for the treatment of sinusitis
INVENTOR(S): Osbakken, Robert S., Camarillo, CA, UNITED STATES
Hale, Mary Anne, Woodland Hills, CA, UNITED STATES
Leivo, Frederick T., Carpinteria, CA, UNITED STATES
Munk, James D., Camarillo, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002061281	A1	20020523
APPLICATION INFO.:	US 2001-942959	A1	20010831 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. WO 2000-US18410, filed on 5 Jul 2000, UNKNOWN Continuation-in-part of Ser. No. US 2000-577623, filed on 25 May 2000, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-142618P	19990706 (60)
	US 1999-142620P	19990706 (60)
	US 1999-142621P	19990706 (60)
	US 1999-142622P	19990706 (60)
	US 1999-142624P	19990706 (60)
	US 1999-142741P	19990706 (60)
	US 1999-142881P	19990706 (60)
	US 2000-193507P	20000403 (60)
	US 2000-193508P	20000403 (60)
	US 2000-193509P	20000403 (60)
	US 2000-193510P	20000403 (60)
	US 2000-194078P	20000403 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MORGAN, LEWIS & BOCKIUS, 1800 M STREET NW, WASHINGTON,
DC, 20036-5869
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 1893
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 6 OF 13 USPATFULL on STN

TI Inactive but immunogenic cytokines, pharmaceutical compositions
containing same, and methods of treating homeostatic disorders
associated with an overproduction of cytokines
AB Cytokines, which are biologically inactive in humans but remain
immunogenic, are used in pharmaceutical compositions to promote a
neutralizing immune response against native cytokines when administered
to a subject in need thereof to treat homeostatic conditions and
disorders associated with an overproduction of cytokines.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2000:94704 USPATFULL
TITLE: Inactive but immunogenic cytokines, pharmaceutical
compositions containing same, and methods of treating
homeostatic disorders associated with an overproduction
of cytokines
INVENTOR(S): Zagury, Daniel, Paris, France
Zagury, Jean-Fran.cedilla.ois, Paris, France
Bizzini, Bernard, Le Mesnil-Saint-Denis, France
PATENT ASSIGNEE(S): Neovacs, Paris, France (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6093405		20000725
	WO 9222577		19921223

APPLICATION INFO.: US 1994-167867 19940627 (8)
 WO 1992-FR544 19920617
 19940627 PCT 371 date
 19940627 PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1991-7399	19910617
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Eisenschenk, Frank C.	
ASSISTANT EXAMINER:	Parkin, Jeffrey S.	
LEGAL REPRESENTATIVE:	Browdy and Neimark	
NUMBER OF CLAIMS:	12	
EXEMPLARY CLAIM:	1	
LINE COUNT:	1296	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 7 OF 13 USPATFULL on STN

TI Diazepinoindoles as phosphodiesterase 4 inhibitors
 AB Diazepinoindoles of formula (I), ##STR1## wherein A is mono- to trisubstituted aryl or heteroaryl, and B is an --OR.sub.1 or --NR.sub.2 R.sub.3 group where R.sub.1, R.sub.2 and R.sub.3 are particularly hydrogen, and racemic forms, enantiomers and pharmaceutically acceptable salts thereof, as phosphodiesterase IV inhibitors, are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 1999:132811 USPATFULL
 TITLE: Diazepinoindoles as phosphodiesterase 4 inhibitors
 INVENTOR(S): Pascal, Yves, Rueil-Malmaison, France
 Jacobelli, Henry, Parray-Vieille-Poste, France
 Calvet, Alain, Ann Arbor, MI, United States
 Payne, Adrian, Westerham, United Kingdom
 Dahl, Svein G., Gif-sur-Yvette, France
 PATENT ASSIGNEE(S): Jouveinal, Fresnes, France (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5972927		19991026
	WO 9736905		19971009
APPLICATION INFO.:	US 1998-952891		19981020 (8)
	WO 1997-FR557		19970327
			19980407 PCT 371 date
			19980407 PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1996-4013	19960329
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Shah, Mukund J.	
ASSISTANT EXAMINER:	Kifle, Bruck	
LEGAL REPRESENTATIVE:	Crissey, Todd M.	
NUMBER OF CLAIMS:	23	
EXEMPLARY CLAIM:	1	
LINE COUNT:	2027	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 8 OF 13 USPATFULL on STN

TI Method of using relaxin as therapeutic or preventing agent
 AB Methods of using relaxin (RLX), a peptide hormone of the insulin family, which has been found to produce effects on the walls of blood vessels, on blood clotting and on blood lipids and electrolytes, per se, and through the stimulation of the synthesis and release of the two powerful

substances: nitric oxide (NO) and atrial natriuretic peptide (ANP), are contemplated whereby RLX is administered to a patient for increasing blood flow, producing dilation of the arteries, influencing blood clotting and fibrinolysis, reducing blood lipids, inducing reduction of blood osmolarity and sodium concentration, and through NO for inhibiting release of histamine from mast cells. RLX is accordingly used as a therapeutic agent in methods for treating arteriosclerosis and vascular diseases, ischemia and thrombosis, hypertension and pregnancy's gestosis, and other diseases, or allergic and inflammatory disorders as dysfunctions in fluid and electrolyte balance.

ACCESSION NUMBER: 1999:110286 USPATFULL
 TITLE: Method of using relaxin as therapeutic or preventing agent
 INVENTOR(S): Bigazzi, Mario, Via del Palmerino No.11, Florence, Italy 50137

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5952296		19990914
	WO 9503822		19950209
APPLICATION INFO.:	US 1995-403878		19950323 (8)
	WO 1994-IT124		19940726
			19950323 PCT 371 date
			19950323 PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	IT 1993-FI143	19930727
	IT 1994-FI36	19940219
	IT 1994-FI39	19940225

DOCUMENT TYPE: Utility
 FILE SEGMENT: Granted
 PRIMARY EXAMINER: Tsang, Cecilia J.
 ASSISTANT EXAMINER: Delacroix-Muirheid, C.
 LEGAL REPRESENTATIVE: McGlew and Tuttle, P.C.
 NUMBER OF CLAIMS: 37
 EXEMPLARY CLAIM: 1
 NUMBER OF DRAWINGS: 15 Drawing Figure(s); 5 Drawing Page(s)
 LINE COUNT: 750

L24 ANSWER 9 OF 13 USPATFULL on STN

TI Triazole derivative and pharmaceutical use thereof
 AB An agent for the prophylaxis and treatment of immune-related diseases, in particular, immunosuppressant, an agent for the prophylaxis and treatment of allergic diseases, an agent for the prophylaxis and treatment of eosinophil-related diseases and an eosinophilia inhibitor, comprising, as an active ingredient, a series of triazole derivatives of the following formula (I) ##STR1## or the following formula (III) ##STR2## wherein each symbol is as defined in the specification, or a pharmaceutically acceptable salt thereof. A novel monocyclic or bicyclic triazole derivative. The agent for the prophylaxis and treatment of immune-related diseases, in particular, immunosuppressant, the agent for the prophylaxis and treatment of allergic diseases, the agent for the prophylaxis and treatment of eosinophil-related diseases, the eosinophilia inhibitor and the novel triazole derivative of the present invention all, have superior eosinophilia-inhibitory action and lymphocyte activation-inhibitory action. They are low toxic and persistent in action. They are particularly effective in the treatment of accumulation and activation of eosinophil and lymphocytes, inflammatory respiratory tract diseases, eosinophil-related diseases such as eosinophilia, and immune-related diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 1998:51621 USPATFULL
 TITLE: Triazole derivative and pharmaceutical use thereof
 INVENTOR(S): Akahoshi, Fumihiko, Osaka, Japan
 Okada, Takehiro, Osaka, Japan
 Takeda, Shinji, Osaka, Japan
 Naito, Youichiro, Osaka, Japan
 Fukaya, Chikara, Osaka, Japan
 Kuwahara, Shigeki, Osaka, Japan
 Kajii, Masahiko, Osaka, Japan
 Nishimura, Hiroko, Osaka, Japan
 Sugiura, Masanori, Osaka, Japan
 PATENT ASSIGNEE(S): The Green Cross Corporation, Osaka, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5750545		19980512
	WO 9503286		19950202
APPLICATION INFO.:	US 1996-586787		19960123 (8)
	WO 1994-JP1215		19940722
			19960123 PCT 371 date
			19960123 PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1993-182522	19930723
	JP 1993-182544	19930723
	JP 1993-193460	19930804
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Raymond, Richard L.	
LEGAL REPRESENTATIVE:	Sughrue, Mion, Zinn, Macpeak & Seas, PLLC	
NUMBER OF CLAIMS:	17	
EXEMPLARY CLAIM:	1	
LINE COUNT:	3304	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 10 OF 13 USPATFULL on STN

TI N-acyl derivatives of aminoalcohols with polycarboxylic acids able to modulate mast cells in inflammatory processes having neuroimmunogenic origin
 AB N-acyl derivatives of aminoalcohols with bicarboxylic or tricarboxylic acids able to modulate the **degranulation** process consequent to the mast cells activation in inflammatory processes caused by supramaximal stimuli of neurogenic and immunogenic origin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 97:29497 USPATFULL
 TITLE: N-acyl derivatives of aminoalcohols with polycarboxylic acids able to modulate mast cells in inflammatory processes having neuroimmunogenic origin
 INVENTOR(S): Della Valle, Francesco, Padua, Italy
 Lorenzi, Silvana, Padua, Italy
 Marcolongo, Gabriele, Carrara San Giorgio, Italy
 PATENT ASSIGNEE(S): Lifegroup S.p.A., Rome, Italy (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5618842		19970408
APPLICATION INFO.:	US 1994-265460		19940624 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1992-998792, filed on 30 Dec 1992, now abandoned		

NUMBER	DATE
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PRIORITY INFORMATION: IT 1991-MI3509 19911231
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Cintins, Marianne
ASSISTANT EXAMINER: MacMillan, Keith
LEGAL REPRESENTATIVE: Watson Cole Stevens Davis, P.L.L.C.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 1384
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 11 OF 13 USPATFULL on STN

TI Use of zinc acexamate in the prophylaxis of gastropathy induced by non-steroidal anti-inflammatory drugs
AB Zinc acexamate acts by increasing the synthesis of mucus, reinforces the mucous barrier, improves the microcirculation and increases the synthesis of prostaglandins in the gastric mucous membrane, whereby it is effective in the treatment of said gastropathy, contrary to the results obtained with antiacids or antisecretory agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 92:63848 USPATFULL
TITLE: Use of zinc acexamate in the prophylaxis of gastropathy induced by non-steroidal anti-inflammatory drugs
INVENTOR(S): Vinas, Antonio B., Barcelona, Spain
PATENT ASSIGNEE(S): Laboratorios Vinas, S.A., Barcelona, Spain (non-U.S. corporation)

NUMBER KIND DATE

PATENT INFORMATION: US 5135925 19920804
APPLICATION INFO.: US 1991-644484 19910118 (7)
RELATED APPLN. INFO.: Continuation of Ser. No. US 1990-505490, filed on 6 Apr 1990, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Friedman, S. J.
LEGAL REPRESENTATIVE: Dressler, Goldsmith, Shore, Sutker & Milnamow, Ltd.
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
LINE COUNT: 357
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 12 OF 13 USPATFULL on STN

TI Injectable glycoproteins containing terminal "C" ends of human immunoglobulins
AB Pharmaceutical compositions comprise, as their essential active ingredients human immunoglobulin D molecules or the terminal C ends of the heavy chains of such molecules, preferably the Fc and F'c fragments. These compositions, which are usually in the form of sterile injectable solutions, have anti-allergic, anti-inflammatory and immunodepressant properties.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 75:70466 USPATFULL
TITLE: Injectable glycoproteins containing terminal "C" ends of human immunoglobulins
INVENTOR(S): Fontaine, Michel J., 448, rue Paradis, 13008 Marseilles, France

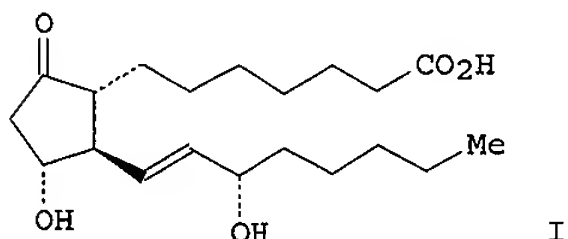
NUMBER KIND DATE

PATENT INFORMATION: US 3928580 19751223

APPLICATION INFO.: US 1974-453019 19740319 (5)

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1973-11455	19730322
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Gotts, Lewis	
ASSISTANT EXAMINER:	Suyat, Reginald J.	
LEGAL REPRESENTATIVE:	Brooks Haidt Haffner & Delahunty	
NUMBER OF CLAIMS:	12	
EXEMPLARY CLAIM:	1	
LINE COUNT:	380	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		

L24 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2003 ACS on STN
TI Effects of prostaglandin E1 on mastocyte degranulation and
heparin liberation elicited by lipid suspensions
GI



AB PGE1 (I) [745-65-3] (3 .times. 10-4M) had a protective effect on the spontaneous degranulation of mastocytes after incubation for 40 min at 37.degree.. However, I decreased but did not prevent the degranulation, accompanied by the liberation of heparin [9005-49-6], in the presence of a lipidic suspension. The action of I was compared with that of cyclic AMP [60-92-4] and cyclic GMP [7665-99-8].

ACCESSION NUMBER: 1980:462034 HCAPLUS
DOCUMENT NUMBER: 93:62034
TITLE: Effects of prostaglandin E1 on mastocyte degranulation and heparin liberation elicited by lipid suspensions
AUTHOR(S): Guillosson, J. J.; Piette, C.; Piette, M.
CORPORATE SOURCE: Lab. d'Hematol., UER Biol. Hum. Exp., Paris, F 75270/6, Fr.
SOURCE: Annales Pharmaceutiques Francaises (1980), 38(1), 15-20
CODEN: APFRAD; ISSN: 0003-4509
DOCUMENT TYPE: Journal
LANGUAGE: French

=> d his

(FILE 'HOME' ENTERED AT 12:49:06 ON 21 NOV 2003)

FILE 'MEDLINE, USPATFULL, WPIDS, JICST-EPLUS, FSTA, HCAPLUS' ENTERED AT 12:53:40 ON 21 NOV 2003

L1 898 S IGE FRAGMENT
L2 59183 S IGE
L3 8710 S CLOSTRIDIUM BOTULINUM
L4 406 S NEISSERIA GONORRHEAE
L5 73853 S FUSION PROTEIN OR HYBRID PROTEIN

L6 719 S MASTOCYTES
 L7 14279 S BASOPHILS
 L8 6169 S TETANUS TOXIN
 L9 5949 S L2 AND L5
 L10 5 S L9 AND L6
 L11 1541 S L3 AND TYPE A
 L12 383 S IGA PROTEASE
 L13 4861 S L2 AND TOXIN
 L14 1816 S L13 AND TRANSPORT
 L15 1 S L14 AND L6
 L16 406 S L14 AND L7
 L17 6 S L16 AND L1
 L18 15947 S DEGRANULATION
 L19 1464 S L18 AND PREVENTION
 L20 147 S L18 AND L6
 L21 1780 S L18 AND L7
 L22 40 S L20 AND INHIBITION
 L23 1032 S L19 AND INHIBITION
 L24 13 S L22 AND L23

=> s IgE () transport () basophil () toxin
 L25 0 IGE (W) TRANSPORT (W) BASOPHIL (W) TOXIN

=> s l2 and allergic response
 L26 1419 L2 AND ALLERGIC RESPONSE

=> s toxin transport
 L27 99 TOXIN TRANSPORT

=> s l27 and l1
 L28 0 L27 AND L1

=> s l2 and transport to basophil
 L29 0 L2 AND TRANSPORT TO BASOPHIL

=> s IgE () transport () basophil
 L30 0 IGE (W) TRANSPORT (W) BASOPHIL

=> s l3 and l2
 L31 317 L3 AND L2

=> s l31 and l18
 L32 9 L31 AND L18

=> d l32 ti abs ibib tot

L32 ANSWER 1 OF 9 MEDLINE on STN
 TI Influence of *Clostridium botulinum* C2 toxin on Fc
 epsilonRI-mediated secretion and tyrosine phosphorylation in RBL cells.
 AB We studied the effects of the binary *Clostridium*
botulinum C2 toxin on stimulated [3H]serotonin release and protein
 tyrosine phosphorylation in RBL 2H3 hml cells. Actin was specifically
 ADP-ribosylated by C2 toxin in intact cells resulting in a 2-3 fold
 increase in antigen- or calcium ionophore (A23187)-induced
 degranulation. The effects of C2 toxin were time- and
 concentration-dependent. Toxin treatment, which dramatically changes the
 morphology of RBL cells, was not sufficient to induce mediator release in
 the absence of activators of secretion. Antigen- and A23187-stimulated
 tyrosine phosphorylation of 60-80 kDa and 110-120 kDa proteins was reduced
 or blocked after C2 toxin incubation. Treatment of RBL cells with the
 tyrosine phosphatase inhibitor pervanadate reversed the inhibitory effect
 of C2 toxin on stimulated protein tyrosine phosphorylation indicating
 activation of phosphatases by C2 toxin. The data indicate that
 disassembly of the actin cytoskeleton by C2 toxin facilitates Fc

epsilonRI-mediated signal-secretion coupling and suggest a role of the actin cytoskeleton in phosphatase regulation in RBL cells.

ACCESSION NUMBER: 1998209675 MEDLINE
DOCUMENT NUMBER: 98209675 PubMed ID: 9550305
TITLE: Influence of *Clostridium botulinum* C2 toxin on Fc epsilonRI-mediated secretion and tyrosine phosphorylation in RBL cells.
AUTHOR: Prepens U; Barth H; Wilting J; Aktories K
CORPORATE SOURCE: Institut fur Pharmakologie und Toxikologie der Albert-Ludwigs-Universitat Freiburg, Germany.
SOURCE: NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, (1998 Mar) 357 (3) 323-30.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980528

L32 ANSWER 2 OF 9 MEDLINE on STN

TI Inhibition of Fc epsilon-RI-mediated activation of rat basophilic leukemia cells by *Clostridium difficile* toxin B (monoglucosyltransferase).
AB Treatment of rat basophilic leukemia (RBL) 2H3-hm1 cells with *Clostridium difficile* toxin B (2 ng/ml), which reportedly depolymerizes the actin cytoskeleton, blocked [3H]serotonin release induced by 2,4-dinitrophenyl-bovine serum albumin, carbachol, mastoparan, and reduced ionophore A23187-stimulated **degranulation** by about 55-60%. In lysates of RBL cells, toxin B 14C-glucosylated two major and one minor protein. By using two-dimensional gel electrophoresis and immunoblotting, RhoA and Cdc42 were identified as protein substrates of toxin B. In contrast to toxin B, *Clostridium botulinum* transferase C3 that selectively inactivates RhoA by ADP-ribosylation did not inhibit **degranulation** up to a concentration of 150 microg/ml. Antigen-stimulated tyrosine phosphorylation of a 110-kDa protein was inhibited by toxin B as well as by the phosphatidylinositol 3-kinase inhibitor wortmannin. Depolymerization of the microfilament cytoskeleton of RBL cells by C. botulinum C2 toxin or cytochalasin D resulted in an increased [3H]serotonin release induced by antigen, carbachol, mastoparan, or by calcium ionophore A23187, but without affecting toxin B-induced inhibition of **degranulation**. The data indicate that toxin B inhibits activation of RBL cells by glucosylation of low molecular mass GTP-binding proteins of the Rho subfamily (most likely Cdc42) by a mechanism not involving the actin cytoskeleton.

ACCESSION NUMBER: 96205904 MEDLINE
DOCUMENT NUMBER: 96205904 PubMed ID: 8631752
TITLE: Inhibition of Fc epsilon-RI-mediated activation of rat basophilic leukemia cells by *Clostridium difficile* toxin B (monoglucosyltransferase).
AUTHOR: Prepens U; Just I; von Eichel-Streiber C; Aktories K
CORPORATE SOURCE: Institut fur Pharmakologie und Toxikologie der Albert-Ludwigs-Universitat Freiburg, Germany.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Mar 29) 271 (13) 7324-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960715
Last Updated on STN: 19980206

L32 ANSWER 3 OF 9 USPATFULL on STN

TI Sphingolipid derivatives and their methods of use

AB Derivatives of sphingolipids of the formula: ##STR1##

are provided wherein the substituents are as defined in the specification and wherein there is at least one R^{sup.2} substituent in the sphingolipid derivative. The compounds are useful in the treatment of abnormal cell proliferation, including benign and malignant tumors, the promotion of cell differentiation, the induction of apoptosis, the inhibition of protein kinase C, and the treatment of inflammatory conditions, psoriasis, inflammatory bowel disease as well as proliferation of smooth muscle cells in the course of development of plaques in vascular tissue. The invention also includes a method for triggering the release of cytochrome c from mitochondria that includes administering an effective amount of a sphingolipid or its derivative or prodrug to a host in need thereof. Further, the invention provides a method for treating bacterial infections, including those that influence colon cancer and other disorders of the intestine, that includes administering an effective amount of one of the active compounds identified herein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:228401 USPATFULL

TITLE: Sphingolipid derivatives and their methods of use

INVENTOR(S): Liotta, Dennis C., McDonough, GA, United States
Merrill, Jr., Alfred H., Stone Mountain, GA, United States

Keane, Thomas E., Dunwoody, GA, United States

Bhalla, Kapil N., Atlanta, GA, United States

Schmelz, Eva M, Atlanta, GA, United States(4)

PATENT ASSIGNEE(S): Emory University, Atlanta, GA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6610835	B1	20030826
APPLICATION INFO.:	US 1999-249211		19990212 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-74536P	19980212 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Wilson, James O.	
ASSISTANT EXAMINER:	Maier, Leigh C.	
LEGAL REPRESENTATIVE:	King & Spalding LLP, Knowles, Sherry M.	
NUMBER OF CLAIMS:	42	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	18 Drawing Figure(s); 16 Drawing Page(s)	
LINE COUNT:	4123	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L32 ANSWER 4 OF 9 USPATFULL on STN

TI Gene products that regulate glucose response in cells

AB The present invention describes the identification of numerous genes, both known and unknown, that play an important role in the ability of cell to respond to glucose stimulation under physiologic conditions. These genes may be used to enhance, stabilize or introduce glucose-responsiveness in a host cell, in particular, a host cell that secretes insulin. In addition, these genes may be used as targets for drug screening and as diagnostic indicators for the loss of glucose-responsiveness.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:213783 USPATFULL
TITLE: Gene products that regulate glucose response in cells
INVENTOR(S): Newgard, Christopher B., Dallas, TX, UNITED STATES
Jensen, Per Bo, Ballerup, DENMARK

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003148421	A1	20030807
APPLICATION INFO.:	US 2002-80381	A1	20020219 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-270251P	20010220 (60)
	US 2001-274706P	20010309 (60)
	US 2001-291354P	20010515 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Steven L. Highlander, Fullbright & Jaworski L.L.P., Suite 2400, 600 Congress Avenue, Austin, TX, 78701	
NUMBER OF CLAIMS:	55	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	12 Drawing Page(s)	
LINE COUNT:	6287	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L32 ANSWER 5 OF 9 USPATFULL on STN

TI Hybrid protein for inhibiting the **degranulation** of mastocytes
and the use thereof

AB A hybrid protein contains a protein that binds to a receptor of
mastocytes and basophils and is endocyted by them. The protein can be
IgE; **IgE** fragment; **IgE** Fc fragment; antibody
against **IgE** receptor of mastocytes and basophils; fragment of
the antibody against the **IgE** receptor of mastocytes and
basophils; antibody against mastocyte specific potassium channel; and
mast cell degranulating peptide. The hybrid protein also contains a
protease cleaving proteins of the secretion process of the mastocytes
and basophils so as to inhibit the secretion process without killing the
mastocytes and basophils. The protease can be light chain
Clostridium botulinum toxin; proteolytically active
fragment of the light chain of a **Clostridium botulinum**
toxin containing an amino acid sequence His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His
wherein Xaa is an amino acid; light chain of the tetanus toxin;
proteolytically active fragment of the light chain of the tetanus toxin
containing His-Asp-Leu-Ile-His-Val-Leu-His; IgA protease of *Neisseria*
gonorrhoeae; and proteolytic domain of the IgA protease of *Neisseria*
gonorrhoeae.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:86306 USPATFULL
TITLE: Hybrid protein for inhibiting the **degranulation**
of mastocytes and the use thereof
INVENTOR(S): Bigalke, Hans, Hannover, GERMANY, FEDERAL REPUBLIC OF
Frevert, Jurgen, Berlin, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): BioteCon Gesellschaft fur biotechnologische Entwicklung
und consulting mbH, Berlin, DE, 10589 (non-U.S.
corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003059912	A1	20030327
APPLICATION INFO.:	US 2002-64903	A1	20020827 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-700540, filed		

on 19 Jan 2001, PENDING A 371 of International Ser. No.
WO 1999-EP3272, filed on 12 May 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1998-19821285	19980513
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	GUDRUN E. HUCKETT, LONSSTR. 53, WUPPERTAL, 42289	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
LINE COUNT:	576	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L32 ANSWER 6 OF 9 USPATFULL on STN

TI Methods for evaluating risk of developing periodontitis

AB The subject invention relates to methods and kits for detecting or evaluating risk of presently or later developing active periodontitis, comprising: (a) collecting gingival crevicular fluid; (b) measuring the amount in the gingival crevicular fluid of IgA; (c) measuring the amount in the gingival crevicular fluid of a marker for polymorphonuclear leukocytes; (d) comparing a ratio of the amounts obtained from steps (b) and (c) to a standard.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 94:112896 USPATFULL

TITLE: Methods for evaluating risk of developing periodontitis

INVENTOR(S): Singer, Jr., Robert E., Fairfield, OH, United States

PATENT ASSIGNEE(S): The Procter & Gamble Company, Cincinnati, OH, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5376532		19941227
APPLICATION INFO.:	US 1992-947657		19920918 (7)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Bidwell, Carol E.		
LEGAL REPRESENTATIVE:	Crosmun, Jean R., Suter, David L., Graff, Mick B.		
NUMBER OF CLAIMS:	6		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1053		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L32 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN

TI Inhibiting the degranulation in mastocytes using a hybrid protein comprising a receptor-binding protein fused to a protease cleaving a protein of the secretion process

AB A hybrid protein is provided contg. a protein that binds to a receptor of mastocytes and basophils and is endocytosed by them. The protein can be IgE, IgE fragment, IgE Fc fragment, antibody against the IgE receptor of mastocytes and basophils, a fragment of the antibody against the IgE receptor of mastocytes and basophils, an antibody against mastocyte-specific potassium channel, or mast cell degranulating peptide. The hybrid protein also contains a protease which cleaves proteins of the secretion process of the mastocytes and basophils so as to inhibit the secretion process without killing the mastocytes and basophils. The protease can be the light chain of Clostridium botulinum toxin or its proteolytic fragments contg. a His-Xaa-Xaa-Xaa-His-Xaa-Xaa-His sequence, the light chain of the tetanus toxin or proteolytically active fragment of the light chain contg. His-Asp-Leu-Ile-His-Val-Leu-His, or an IgA protease of Neisseria gonorrhoeae and its proteolytic domain. Thus, a hybrid protein comprising IgE fused to the light chain of either Clostridium

botulinum toxin or tetanus toxin prevents allergic shock caused by dying mastocytes.

ACCESSION NUMBER: 2003:241912 HCAPLUS
DOCUMENT NUMBER: 138:265639
TITLE: Inhibiting the **degranulation** in mastocytes
using a hybrid protein comprising a receptor-binding
protein fused to a protease cleaving a protein of the
secretion process
INVENTOR(S): Bigalke, Hans; Frevert, Jurgen
PATENT ASSIGNEE(S): Biotecon Gesellschaft Fur Biotechnologische
Entwicklung Und Consulting Mbh, Germany
SOURCE: U.S. Pat. Appl. Publ., 7 pp., Cont.-in-part of U.S.
Ser. No. 700,540.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003059912	A1	20030327	US 2002-64903	20020827
WO 9958571	A2	19991118	WO 1999-EP3272	19990512
WO 9958571	A3	20000203		
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: DE 1998-19821285 A 19980513
WO 1999-EP3272 W 19990512
US 2001-700540 A2 20010119

L32 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN

TI Hybrid protein for inhibiting the **degranulation** of mastocytes and the use thereof

AB The invention relates to a hybrid protein comprising or comprised of (i) a known protein which binds to mastocytes and/or basophils in a known manner and/or is absorbed thereby, and of (ii) a protease which splits one or more proteins of the secretory app. of the mastocytes and/or basophils. The examples discuss the synthesis of these hybrid proteins using expression vectors expressed in E. coli.

ACCESSION NUMBER: 1999:736768 HCAPLUS
DOCUMENT NUMBER: 131:332099
TITLE: Hybrid protein for inhibiting the
degranulation of mastocytes and the use
thereof
INVENTOR(S): Bigalke, Hans; Frevert, Jurgen
PATENT ASSIGNEE(S): Biotecon Gesellschaft fur Biotechnologische
Entwicklung und Consulting m.b.H, Germany
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958571	A2	19991118	WO 1999-EP3272	19990512

WO 9958571 A3 20000203

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,
DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2331274 AA 19991118 CA 1999-2331274 19990512

AU 9942605 A1 19991129 AU 1999-42605 19990512

AU 755513 B2 20021212

BR 9910359 A 20010109 BR 1999-10359 19990512

EP 1084146 A2 20010321 EP 1999-950347 19990512

EP 1084146 B1 20021113

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI

JP 2002514659 T2 20020521 JP 2000-548373 19990512

AT 227739 E 20021115 AT 1999-950347 19990512

ES 2187200 T3 20030516 ES 1999-950347 19990512

RU 2214420 C2 20031020 RU 2000-131217 19990512

NO 2000005637 A 20001108 NO 2000-5637 20001108

HK 1036994 A1 20030221 HK 2001-106685 20010921

US 2003059912 A1 20030327 US 2002-64903 20020827

PRIORITY APPLN. INFO.: DE 1998-19821285 A 19980513

WO 1999-EP3272 W 19990512

US 2001-700540 A2 20010119

L32 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN

TI Influence of *Clostridium botulinum* C2 toxin on
Fc.epsilon.RI-mediated secretion and tyrosine phosphorylation in RBL cells

AB The authors studied the effects of the binary *Clostridium*
botulinum C2 toxin on stimulated [3H]serotonin release and protein
tyrosine phosphorylation in RBL 2H3 hml cells. Actin was specifically
ADP-ribosylated by C2 toxin in intact cells resulting in a 2-3 fold
increase in antigen- or calcium ionophore (A23187)-induced
degranulation. The effects of C2 toxin were time- and
concn.-dependent. Toxin treatment, which dramatically changes the
morphol. of RBL cells, was not sufficient to induce mediator release in
the absence of activators of secretion. Antigen- and A23187-stimulated
tyrosine phosphorylation of 60-80 kDa and 110-120 kDa proteins was reduced
or blocked after C2 toxin incubation. Treatment of RBL cells with the
tyrosine phosphatase inhibitor pervanadate reversed the inhibitory effect
of C2 toxin on stimulated protein tyrosine phosphorylation indicating
activation of phosphatases by C2 toxin. The data indicate that
disassembly of the actin cytoskeleton by C2 toxin facilitates
Fc.epsilon.RI-mediated signal-secretion coupling and suggest a role of the
actin cytoskeleton in phosphatase regulation in RBL cells.

ACCESSION NUMBER: 1998:137930 HCAPLUS

DOCUMENT NUMBER: 128:267074

TITLE: Influence of *Clostridium botulinum*
C2 toxin on Fc.epsilon.RI-mediated secretion and
tyrosine phosphorylation in RBL cells

AUTHOR(S): Prepens, Ulrike; Barth, Holger; Wilting, Jorg;
Aktories, K.

CORPORATE SOURCE: Institut fur Pharmakologie und Toxikologie der
Albert-Ludwigs-Universitat Freiburg,
Hermann-Herder-Strasse 5, Freiburg, D-79104, Germany

SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1998),
357(3), 323-330

CODEN: NSAPCC; ISSN: 0028-1298

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT:

59

THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

WEST**Freeform Search****Database:**

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 US Pre-Grant Publication Full-Text Database
 JPO Abstracts Database
 EPO Abstracts Database
 Derwent World Patents Index
 IBM Technical Disclosure Bulletins ▼

Term:

inhibition same degraulation mastocyte

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result set*DB=USPT; PLUR=YES; OP=OR*

<u>L11</u>	L10 and l5	59	<u>L11</u>
<u>L10</u>	L9 and inhibit degranulation	53547	<u>L10</u>
<u>L9</u>	hybrid protein and binding receptor	166550	<u>L9</u>
<u>L8</u>	clostridium botulinum toxin and L7	15971	<u>L8</u>
<u>L7</u>	tetanus toxin and L6	17220	<u>L7</u>
<u>L6</u>	l5 and hybrid protein	141489	<u>L6</u>
<u>L5</u>	inhibition same degraulation mastocyte	91	<u>L5</u>
<u>L4</u>	inhibition same degraulation same mastocyte	0	<u>L4</u>
<u>L3</u>	inhibition near degraulation near mastocyte	0	<u>L3</u>
<u>L2</u>	inhibition and degraulation and mastocyte	0	<u>L2</u>
<u>L1</u>	inhibition adj degraulation adj mastocyte	0	<u>L1</u>

END OF SEARCH HISTORY

WEST

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L11: Entry 1 of 59

File: USPT

Nov 18, 2003

DOCUMENT-IDENTIFIER: US 6649166 B1

TITLE: Peptides and proteins for desensitizing subjects allergic to bee venom and compositions containing sameAbstract Text (1):

The invention concerns peptides and proteins for desensitizing specifically the vast majority of subjects allergic to bee venom and compositions containing said peptides or proteins. The peptides are selected in the group consisting of: the fragment (1) corresponding to positions P85-97 of the major bee venom allergen, the fragment (2) corresponding to positions P81-93 of the major bee venom allergen, the fragment (3) corresponding to positions P94-106 of the major bee venom allergen, the fragment (4) corresponding to positions P76-88 of the major bee venom allergen, the fragment (5) corresponding to positions P77-94 of the major bee venom allergen, and the fragment (6) corresponding to positions P122-134 of the major bee venom allergen, fragments (I) and (2) forming group (I); fragment (3) forming group (II); fragments (4) and (4) forming group (III) and fragment (6) forming group IV and the mutated fragments of said fragments (1) to (6) which have a binding activity with MHC class (II) molecules identical or higher than those of said fragments (1) to (6). The invention also concerns compositions containing said peptides or proteins.

Brief Summary Text (1):

The present invention relates to peptides and proteins capable of desensitizing, in a specific manner, the great majority of subjects allergic to bee venom, and to compositions containing said peptides or proteins.

Brief Summary Text (4):

IgEs appear gradually under the repeated action of stings and before any symptom becomes apparent. Although the bee venom comprises numerous peptides and proteins, all the components do not appear to be allergenic (4). Melittin, for example, induces IgEs in only 30% of patients, whereas the proportion increases to more than 90% for phospholipase A2 (PLA2) which is, as a result, considered to be the major allergen (API m1). The protein sequence of bee venom phospholipase A2 (API m1) is illustrated in FIG. 1 (SEQ ID NO: 8); this sequence is deduced from that of the complementary cDNA (36).

Brief Summary Text (5):

IgEs possess the property of binding, via their Fc fragment, to receptors situated on the tissue mastocytes and the blood basophils. When the allergen forms a complex with the specific IgEs bound to the membrane of the basophils or mastocytes, it causes degranulation of the cells and the release of molecules which are responsible for the principal manifestations observed during an allergic accident. IgEs are not solely responsible for the allergy because although the IgE level is an indicator for the disease, it has no diagnostic value for the state of the patients. It is not rare for patients to have high IgE levels without showing symptoms. The appearance of IgEs in allergic patients results from the production of type TH2 cytokines such as IL-4, IL-5 and IL-13 and is inhibited by the synthesis of IFN- γ . (6).

Brief Summary Text (9):

The CD4^{sup.} + T lymphocytes possess a rearranged T receptor which allows them to selectively recognize peptide fragments derived from the degradation of the antigen by the presenting cells and presented by the Major Histocompatibility Complex class II (MHC II) molecules (15). The determinants which these peptide fragments carry and which the T lymphocytes effectively recognize are called T epitopes.

Brief Summary Text (11):

It has indeed been observed in vivo in mice for the allergens Fel d1 (cat hair), Der p1 (acarian: Dermatophagoides pterissimus) and Bet v1 (birch pollen) that the nasal, oral or subcutaneous administration of peptides carrying T epitopes of these allergens inhibits the activation of the specific T lymphocytes (16-18) and modulates the allergic reaction (16, 18).

Brief Summary Text (13):

Several types of molecule are already being studied, including in the context of bee venom allergy and consist either of peptide fragments or of modified proteins.

Brief Summary Text (22):

The approach followed by these various authors (23, 24 and 30) is based on cellular tests and not on binding tests. The results observed show that the active peptides vary according to the patients. In the latter three studies, the peptides containing the zone 80-90 are those which are most often a T epitope. They also show that the lymphocytes of several patients are stimulated by peptides containing the C-terminal portion of API m1.

Brief Summary Text (25):Modified ProteinsBrief Summary Text (30):

The molecules of the major histocompatibility complex (MHC) class II (HLA II in man) are heterodimers expressed on presenting cells and present the T epitopes of the antigens to the CD4^{sup}.+ T lymphocytes. These molecules are capable of binding a large repertoire of peptides having very different sequences, which allows them to present several peptides per antigen to the T cells.

Brief Summary Text (32):

Each allele possesses its own binding properties. It therefore binds a repertoire of peptides specific to it and which differs from that for another allele, even on the same antigen. The broad specificity of the HLA II molecules and the existence of several isoforms and of a high polymorphism mean that many different fragments of the antigen can be presented to the T lymphocytes.

Brief Summary Text (35):

The 2nd gene encodes the HLA-DRB3, -DRB4 and -DRB5 molecules which are HLA-DR molecules whose .beta. chain is not encoded by the DRB1 gene. Although less well known than the molecules derived from the 1st gene, these HLA molecules are functional and are capable of presenting peptides to the T lymphocytes (56-59). Their main advantage for the immunotherapy is that alleles such as DRB3*0101 (9.2%), DRB4*0101 (28.4%) and DRB5*0101 (7.9%) are very frequent in the Caucasian population. They cover, on their own, 45% of the gene frequency. They are systematically associated with another HLA-DR molecule and can therefore complement its specificity. A strong binding disequilibrium exists between the 1st and 2nd gene, that is to say that a 2nd gene is very often associated with particular alleles of the 1st gene. The set of DR pseudogene and genes present on the same chromosome constitutes a DR haplotype (FIG. 5). Each haplotype is defined by the second DR molecule which characterizes it.

Brief Summary Text (39):

The subject of the present invention is peptides capable of desensitizing a subject allergic to bee venom, characterized in that they are selected from the group consisting of: fragment (1) corresponding to positions P85-97 of the major bee venom allergen, fragment (2) corresponding to positions P81-93 of the major bee venom allergen, fragment (3) corresponding to positions P94-106 of the major bee venom allergen, fragment (4) corresponding to positions P76-88 of the major bee venom allergen, fragment (5) corresponding to positions P77-94 of the major bee venom allergen, fragment (6) corresponding to positions P122-134 of the major bee venom allergen, and the mutated fragments of said fragments (1) to (6) which exhibit an MHC class II molecule binding activity identical to or higher than those of said fragments (1) to (6).

Brief Summary Text (43):

The site for binding of the peptides to the class II molecules is situated between the .alpha. helices of the .alpha.1 and .alpha.2 domains and forms a groove which is open at both ends. This opening allows the binding of peptides with varying sizes, in general from 13 to 25 amino acids. The anchoring of the peptides to the MHC II molecules occurs by means of hydrogen bonds between the backbone of the peptide and the amino acids of the groove and by means of residues accommodated by pockets for specificity. Five pockets, called P1, P4, P6, P7 and P9, correspond to the amino acid of the peptide which it accommodates, the first position being that which is in the first pocket, receive amino acids of the peptide and are composed of conserved or polymorphic residues. The polymorphic residues are responsible for various specificities between MHC II molecules. Since the binding site is open, two peptides binding one MHC II molecule may do so according to different modes, that is to say using different anchoring residues in their sequence.

Brief Summary Text (45):

In order to be able to introduce residues which preserve or increase the binding activity, the modes of interaction of the peptides P81-93 and P85-97 with respect to the HLA-DR molecules capable of binding them were studied. The approach chosen was to introduce into each position an alanine so as to evaluate the role of the side chain in the interaction or a lysine which is a basic and bulky amino acid. If necessary, a combination of mutations was introduced. By way of example, a reduction in activity caused by substitutions of phenylalanine 88 by a lysine or an alanine is observed in FIG. 6. Other reductions in activity are observed at positions situated at 3, 5 and 8 amino acids from phenylalanine 88. This activity profile corresponds to a mode of binding where positions F88, I91 T93 and Y96 are accommodated by the pockets P1, P4, P6 and P9, respectively, of the molecules HLA-DRB3*0101, HLA-DRB5*0101, HLA-DRB1*1301 and HLA-DRB1*0701. This mode of association was confirmed by molecular modeling for the complexes: P85-97/DRB3*0101, P85-97/DRB5*0101 and P81-93/DRB4*0101. All the results are given in FIG. 7. It is observed that on sequence 81-97, there are at least six modes of binding to the HLA-DR molecules. It is also observed that mode I is common to eight molecules whereas modes V and VI are specific to a single molecule.

Brief Summary Text (52):

The subject of the present invention is also desensitizing compositions for bee venom allergies, characterized in that they comprise: at least one peptide selected from group A consisting of: the peptides of group I, as defined above, and the peptides consisting of fragments of at least 13 amino acids which are included in or comprise the fragment corresponding to positions P81-97 of the major bee venom allergen (API m1) and which bind at least to the HLA-DR molecules encoded by the HLA alleles DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701, DRB1*1101, DRB1*1301 and DRB1*1501 (molecules DR1, DR3, DR4, DR7, DR11, DR13 and DR2), with a binding activity <1000 nM, and at least one pharmaceutically acceptable vehicle.

Brief Summary Text (54):

According to an advantageous embodiment of said compositions, they preferably consist of a mixture of peptides comprising: at least one group A peptide as defined above and at least one other peptide selected from the following groups: the peptides selected from group B consisting of: the peptides of group II, as defined above, and the peptides consisting of fragments of at least 13 amino acids which are included in or comprise the fragment corresponding to positions 94-106 of the major bee venom allergen (API m1) and which bind at least to the HLA-DR molecules expressed by the alleles DRB1*0101, DRB1*0401 and DRB1*1101 (molecules DR1, DR4 and DR11), with a binding activity <1000 nM, the peptides selected from group C consisting of: the peptides of group III, as defined above, and the peptides consisting of fragments of at least 13 amino acids which are included in or comprise the fragment corresponding to positions P76-94 of the major bee venom allergen and which bind at least to the HLA-DR molecules expressed by the alleles DRB1*0701, DRB1*1101 and DRB1*1501 (molecules DR7, DR11 and DR2), with a binding activity <1000 nM, and the peptides selected from group D consisting of: the peptides of group IV, as defined above, and the peptides consisting of fragments of at least 13 amino acids which are included in or comprise the fragment corresponding to positions P122-134 of the major bee venom allergen and which bind at least to the HLA-DR molecules expressed by the alleles DRB1*1101, DRB1*1301 and DRB1*1501 (molecules

DR11, DR13 and DR2), with a binding activity <1000 nM.

Brief Summary Text (59):

These desensitizing compositions are defined from the activities for binding to the HLA-DR molecules of the peptides which they comprise, from the frequency of alleles toward which they are active and from the complementarity of the zones for interaction or epitopes which said peptides carry.

Brief Summary Text (63):

The peptides included in said compositions were advantageously selected using an HLA-DR/peptide binding test comprising (i) incubating the purified HLA-DR molecules selected from those relating to more than 5% of a given population and in particular the HLA molecules DR1, DR3, DR4, DR7, DR11, DR13 and DR2, simultaneously with various concentrations of fragments of 13 to 18 amino acids which overlap and which completely cover the API m1 sequence and with a reagent R1 consisting of a peptide fragment combined with a nonradioactive marker, such as biotin and whose sequence is different from said peptides and is chosen such that it exhibits affinity toward the chosen HLA-DR molecule, such that it can be used at a concentration <200 nM, (ii) transferring the complexes obtained on an ELISA-type plate, previously sensitized with an antibody specific for all the HLA-DR molecules, (iii) revealing the HLA-DR molecules/R1 reagent complexes, attached to the bottom of the plate by means of suitable conjugates, such as streptavidin-phosphatase and a fluorescent substrate, (iv) selecting the peptides comprising different epitopes, that is to say the most representative of the various zones of interaction between the major bee venom allergen and the HLA-DR molecules and (v) choosing the most suitable peptides as a function of the frequency of the alleles toward which they exhibit a binding activity <1000 nM, corresponding to the concentration of this peptide which inhibits 50% of the binding of the reagent R1 (IC.sub.50).

Brief Summary Text (64):

These tests make it possible, unambiguously, to combine with each allele of the 1st gene or of the 2nd gene, the sequences of the fragments capable of binding thereto or on the contrary which do not bind thereto.

Brief Summary Text (67):

Thus, the inventors have found that only some peptides have a binding activity with respect to several of the most frequent alleles in the Caucasian population in accordance with Tables IIIa and IIIb.

Brief Summary Text (71):

The peptides which can be included in a desensitizing composition for bee venom allergies may be advantageously selected by a method which comprises: (i) incubating the purified HLA-DR molecules selected from those relating either to less than 5% of a given population, that is to say those consisting of HLA-DRs other than the HLA molecules DR1, DR3, DR4, DR7, DR11, DR13 and DR2, or HLA-DR molecules from a given patient, simultaneously with various concentrations of fragments of 13 to 18 amino acids which overlap and which completely cover the API m1 sequence and with a reagent R1 consisting of a peptide fragment combined with a nonradioactive marker such as biotin and whose sequence is different from the peptides, as defined above (groups A to D) and is chosen so that it exhibits affinity toward the chosen HLA-DR molecule, such that it can be used at a concentration <200 nM, (ii) transferring the complexes obtained on a microtiter plate, previously sensitized with an antibody specific for all the HLA-DR molecules, (iii) revealing the HLA-DR molecules/R1 reagent complexes, attached to the bottom of the plate by means of suitable conjugates, such as streptavidin-phosphatase and a fluorescent substrate, (iv) selecting the peptides comprising different epitopes, that is to say the most representative of the various zones of interaction between the major bee venom allergen and the HLA-DR molecules studied and (v) choosing the most suitable peptides as a function of the frequency of the alleles toward which they exhibit a binding activity <1000 nM, corresponding to the concentration of this peptide which inhibits 50% of the binding of the reagent R1 (IC.sub.50).

Brief Summary Text (75):

To study the HLA-DR molecules (2nd gene), this requires appropriate pairs of biotinylated peptides which should bind the preparation at low concentration and be

selective for one of the two molecules. More precisely, the binding of the biotinylated peptides should be effectively inhibited by their nonbiotinylated homolog, but not greatly disrupted by the nonbiotinylated form of the other peptide (Table X). It has been possible to find such peptides for each of the molecules DRB3*0101, DRB4*0101 or DRB5*0101.

Drawing Description Text (2):

FIG. 1 represents the protein sequence of bee venom phospholipase A2 (API m1) (SEQ ID NO: 8), deduced from that of the complementary DNA,

Drawing Description Text (3):

FIG. 2 illustrates the activity for binding to the HLA-DR molecules of the peptides of thirteen amino acids which cover sequence 15-37 of the major bee venom allergen. The results are expressed in the 1/IC.sub.50 form. The unit is M.sup.-1 ;

Drawing Description Text (4):

FIG. 3 illustrates the activity for binding to the HLA-DR molecules of the peptides of thirteen amino acids which cover sequence 107-134 of the major bee venom allergen. The results are expressed in the 1/IC.sub.50 form. The unit is M.sup.-1 ;

Drawing Description Text (8):

FIG. 7 illustrates the modes of binding of the sequence 81-97 to the HLA-DR molecules. The blocks schematically represent the site of binding of the HLA-DR molecules which characterize the pockets P1, P4, P6, P7 and P9. A color and a number in Roman numeral was attributed to each mode so as to facilitate their visualization; and

Detailed Description Text (3):

Principle of the Binding Tests

Detailed Description Text (8):

The hybridomas secreting a monomorphic antibody specific for the HLA-DR molecules is in particular that described in Southwood et al. (52) or that described in Posch et al. (42). The antibodies are purified from culture supernatants on Protein A-Sepharose columns. These antibodies are coupled onto Sepharose 4B or Protein A-Sepharose columns for the purification of the HLA-DR molecules.

Detailed Description Text (9):

Tests for HLA-DR/Peptide Binding

Detailed Description Text (10):

The tests for binding of the peptides to the HLA-DR molecules are competition tests with immunoenzymatic visualization, initially developed by Hill on the HLA-DR molecule (37). They are carried out in 96-well plates, which makes it possible to study numerous samples in the same experiment. Briefly, the purified HLA-DR molecules are incubated with a biotinylated peptide which serves as tracer and various concentrations of the peptide to be tested.

Detailed Description Text (11):

After incubating for 24 to 72 hours, the samples are neutralized, and then 100 .mu.l of each sample are transferred onto an ELISA plate previously sensitized by the monomorphic antibody specific for the HLA-DR molecules. The HLA-DR molecules/biotinylated peptide complexes attached at the bottom of the plate via the monomorphic antibody specific for the HLA-DR molecules are visualized by means of the streptavidin-phosphatase conjugate and a fluorescent substrate. The activity of each peptide is characterized by the concentration of this peptide which inhibits the binding of the biotinylated peptide by 50% (IC.sub.50).

Detailed Description Text (12):

Choice and Optimization of the Binding Tests

Detailed Description Text (19):

The choice of the biotinylated peptides is the key element in the specificity of the test. Most of the cells used possess two different HLA-DR molecules which are both purified by a monomorphic antibody specific for the HLA-DR molecules and both are

recognized by the same antibody. In order to unambiguously study the binding of a peptide to the DRB1 allele, it is necessary to ensure that the biotinylated peptide binds this allele and does not bind the product of the other gene.

Detailed Description Text (21):

For HLA-DRB1*0101, DRB1*0401 and DRB1*1101, the peptide ha 306-318 which other authors had previously used in tests for binding to these alleles (37, 41), was used.

Detailed Description Text (27):

Activity for binding to the HLA-DR molecules of the peptides of eighteen amino acids which cover the sequence of the major bee venom allergen (SEQ ID NO: 8).

Detailed Description Text (33):

The peptides which are naturally present on the HLA-DR molecules have sizes which vary between 13 and 25 amino acids approximately, the size most frequently encountered being 15 amino acids. In order to optimize the search for the peptides of API m1 which are capable of binding to the HLA-DR molecules, we synthesized thirty peptides of 18 amino acids which overlap by 14 amino acids and which therefore contain all the peptides of 15 possible residues of the API m1 sequence. The binding capacities of each of these peptides were tested on the 7 alleles which we selected and are expressed in the IC.sub.50 form (Table VII).

Detailed Description Text (35):

Clearly, each allele possesses a profile for binding of the peptides of API m1 which is specific to it. Some peptides bind to only one allele (for example P105-122 to allele 401, P69-86 and P73-90 to allele 1301). Others, by contrast, bind to several alleles. That is the case in particular for peptide P81-98 which significantly binds the seven alleles studied and for peptide P85-102 which significantly binds six alleles. In many cases, a peptide is common to two or several alleles. These common peptides define mainly three distinct zones of the API m1 sequence: i) an N-terminal part which the peptides P13-30, P17-34, P21-38 form, ii) a central part consisting of the peptides P77-94 to P93-110 and iii) a C-terminal part which includes the peptides P113-122 to P117-134. It is also observed that thirteen peptides out of the thirty tested have binding activities >1000 nM, regardless of the MHC II molecule studied. They are therefore inactive or not very active.

Detailed Description Text (36):

Table VIII below illustrates the activity for binding to the HLA-DR molecules of the peptides of 13 amino acids which cover the zone 73-108 of API m1.

Detailed Description Text (37):

Activity for binding to the HLA-DR molecules of the peptides of 13 amino acids which cover the zone 73-108 of the major bee venom allergen (SEQ ID NO: 8).

Detailed Description Text (42):

11 peptides which exhaustively cover the N-terminal part 15 to 37 were tested on the alleles 101, 401, 701, 1101 and 1301 (FIG. 2). For the allele 701, the peptides P18-30 to P22-34 exhibit a significant binding activity which, in the case of the peptide P18-30, is equivalent to that of the peptide of eighteen amino acids P21-38.

Detailed Description Text (43):

The alleles 401, 101 and 1101 substantially bind the same peptides as the allele 701. However, the binding activities observed are lower, which is in agreement with those obtained for the peptides of eighteen amino acids.

Detailed Description Text (44):

The central part was studied on the seven alleles by means of twenty-four peptides of thirteen residues. For the allele 101, the peptides P85-97, on the one hand, and P91-103 to P95-107, on the other hand, define two distinct zones of interaction. These two zones are also found for the alleles 401 and 1101 but with small variations. The first comprises, in addition to the peptide P85-97, the peptides P82-94 and P83-95 for the allele 401 and the peptide P83-95 for the allele 1101. The second zone of contact is strictly identical between the allele 401 and 101 whereas

it is reduced to a single peptide (P94-106) for the allele 1101. The allele 701 is characterized by three peptides having good binding activity (P85-97, P86-98 and P87-99) which corresponds to that of the peptides of eighteen amino acids P81-98 and P85-102. The good activity for binding of the peptide P77-94 to the allele 701 previously described is not observed for any of the peptides of thirteen residues which cover this zone, the peptides P76-88 to P81-93 having a substantially lower activity.

Detailed Description Text (45):

The peptide P85-97 possesses, for the alleles 301 and 1301, a binding activity similar to that of the peptides of 18 amino acids P81-98 and P85-102, containing it. The allele 1301 also accepts the peptide P86-105 as ligand. For the allele 1501, seven peptides, including six which are consecutive (P73-85 to P78-90) and one which is isolated (P81-93) reflect the activity of the three peptides of eighteen amino acids (P73-90, P77-94 and P81-98)

Detailed Description Text (47):

These results describe the precise location of the binding determinants of the major bee venom allergen for the seven alleles chosen and clearly show the differences and the similarities between the alleles for the various peptides of API m1. In order to better account for the activity and the location of these determinants, a representative peptide, which is as short as possible and whose binding activity reflects that of the determinant (Table III) was chosen for each of them. It will be noted most particularly that the peptide P85-97 is representative of a determinant for the alleles 101, 401, 1101, 701, 301 and 1301 and that other determinants are advantageously situated near this peptide (P76-88, P77-94, P81-93, P94-106).

Detailed Description Text (49):

To evaluate the impact of the most active peptides (activity less than 1000 nM) within the Caucasian population, the cumulative frequency of the alleles which they are capable of binding (FIG. 4) was calculated for each. Applied to all the peptides of 18 amino acids which completely cover the sequence of the major allergen, this representation makes it possible to weight the activity of the peptides tested. It is clearly observed that the central zone ranging from the peptide P77-94 to the peptide P93-110 is that which has the greatest impact in the population. The peptide P81-98 binding with a good affinity to all the HLA-DRs studied, covers on its own 63% of the population and combines the impact of the determinants carried by the peptides P85-97 and P81-93. The addition of sequences at the N- and C-terminals makes it possible to add to this combination of determinants other zones of interaction such as P76-88, P77-94 and P93-106 which relate to nonnegligible percentages of the population. Finally, the impact of the peptides P117-134 or 122-134 greater than 20% is observed at the C-terminal.

Detailed Description Text (52):

The peptides which bind to the HLA molecules are not necessarily stimulating for the T lymphocytes. They can indeed resemble self-peptides, such that no T lymphocyte will be capable of recognizing them. On the other hand, it has previously been shown that all the peptides which stimulate the T lymphocytes are part of the best peptides which bind to the MHC II molecules (60). The binding to the MHC II molecules is therefore a necessary but insufficient condition for allowing a peptide to be recognized by the T lymphocytes. In order to verify that the peptides which were identified are effectively capable of stimulating T lymphocytes in allergic patients, their stimulating capacity was tested (FIG. 8). The cells used are peripheral blood cells from people allergic to bee venom. These people came to the Rothschild Hospital to be desensitized and agreed to participate in this study (DGS No. 980457). Given the small number of cells, the peptides were grouped into different pools. The cells from one patient did not result in any proliferation (not shown). Of the six patients for whom reactivity was observed, a high variability was observed in the intensity of the response to the peptides, in the nature and the number of active peptides. However, it is observed that of the 6 patients, 5 respond to pool 7 which comprises peptides which cover zone 77-111 and 3 respond to pool 9 which covers zone 105-134.

Detailed Description Paragraph Table (3):

TABLE VI Protein Tracer concen- concen- Incubation tration tration Optimum time

Alleles (.mu.g/ml) Tracers (nM) pH (h) DRB1*0101 0.6 HA 306-318 10 6 24 DRB1*0301
 2.3 MT 2-016 50 4.5 72 DRB1*0401 1.6 HA 306-318 30 6 24 DRB1*0701 0.4 YKL 10 5 24
 DRB1*1101 1.3 HA 306-318 20 5 24 DRB1*1301 0.7 B1 21-36 200 4.5 72 DRB1*1501 0.5 A3
 152-166 10 4.5 24

Detailed Description Paragraph Table (6):

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 Arg 20 25 30 Thr His Asp Met Cys Pro Asp Val Met Ser Ala Gly Glu Ser Lys His 35 40
 45 Gly Leu Thr Asn Thr Ala Ser His Thr Arg Leu Ser Cys Asp Cys Asp 50 55 60 Asp Lys
 Phe Tyr Asp Cys Leu Lys Asn Ser Ala Asp Thr Ile Ser Ser 65 70 75 80 Tyr Phe Val Gly
 Lys Met Tyr Phe Asn Leu Ile Asp Thr Lys Cys Tyr 85 90 95 Lys Leu Glu His Pro Val Thr
 Gly Cys Gly Glu Arg Thr Glu Gly Arg 100 105 110 Cys Leu His Tyr Thr Val Asp Lys Ser
 Lys Pro Lys Val Tyr Gln Trp 115 120 125 Phe Asp Leu Arg Lys Tyr 130

Other Reference Publication (1):

Dierdre O'Sullivan et al., "Characterization of the Specificity of Peptide Binding
 To Four DR Haplotypes", J. Immunol., 1990, vol. 145, No. 6, pp. 1799-1808.

Other Reference Publication (6):

Alexander Faith et al., "An Altered Peptide Ligand Specifically Inhibits Th2
 Cytokine Synthesis by Abrogating TCR Signaling", J. Immunol., vol. 162, No. 3, Feb.
 1, 1999, pp. 1836-1842.

CLAIMS:

1. A polypeptide molecule capable of desensitizing a human subject to bee venom, the
 polypeptide selected from the group consisting of: (a) a polypeptide molecule
 corresponding to amino acid positions 85-97 of SEQ ID NO: 8; (b) a polypeptide
 molecule corresponding to amino acid positions 81-93 of SEQ ID NO: 8; (c) a
 polypeptide molecule corresponding to amino acid positions 94-106 of SEQ ID NO: 8;
 (d) a polypeptide molecule corresponding to amino acid positions 76-88 of SEQ ID NO:
 8; (e) a polypeptide molecule corresponding to amino acid positions 77-94 of SEQ ID
 NO: 8; (f) a polypeptide molecule corresponding to amino acid positions 122-134 of
 SEQ ID NO: 8; and (g) a polypeptide molecule of (a)-(f) comprising at least one
 amino acid substitution, wherein the substituted polypeptide exhibits binding
 activity to MHC class II molecules identical to or greater than that of the
 polypeptides (a)-(f).

5. A pharmaceutical composition for desensitizing a human subject to bee venom, the composition comprising: at least one polypeptide molecule corresponding to amino acid positions 85-97 of SEQ ID NO: 8 or to amino acid positions 81-93 of SEQ ID NO: 8; at least one polypeptide molecule of at least 13 amino acids and corresponding to a consecutive amino acid sequence within the range of amino acid positions 81-97 of SEQ ID NO: 8 and which binds to at least one HLA-DR molecule encoded by the HLA alleles DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701, DRB1*1101, DRB1*1301 or DRB1*1501 with a binding activity <1000 nM; and at least one pharmaceutically acceptable vehicle.

6. A pharmaceutical composition for desensitizing a human subject to bee venom comprising: (a) at least one polypeptide molecule corresponding to amino acid positions 85-97 of SEQ ID NO: 8 or to amino acid positions 81-93 of SEQ ID NO: 8; (b) at least one polypeptide molecule of at least 13 amino acids and corresponding to a consecutive amino acid sequence within the range of amino acid positions 81-97 of SEQ ID NO: 8 and which binds to at least one HLA-DR molecule encoded by the HLA alleles DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701, DRB1*1101, DRB1*1301 or DRB1*1501 with a binding activity <1000 nM; (c) at least one polypeptide molecule corresponding to amino acid positions 94-106 of SEQ ID NO: 8 or a polymer thereof; (d) at least one polypeptide molecule of at least 13 amino acids and corresponding to a consecutive amino acid sequence within the range of amino acid positions 94-106 of SEQ ID NO: 8, the molecule binding to at least one HLA-DR molecule encoded by the alleles DRB1*0101, DRB1*0401 or DRB1*1101 with a binding activity <1000 nM; (e) at least one polypeptide molecule corresponding to amino acid positions 76-88 or 77-94 of SEQ ID NO: 8 or a polymer thereof; (f) at least one polypeptide molecule of at least 13 amino acids and corresponding to a consecutive amino acid sequence within the range of amino acid positions 76-94 of SEQ ID NO: 8, the molecule binding to at least one HLA-DR molecule encoded by the alleles DRB1*0701, DRB1*1101 or DRB1*1501 with a binding activity <1000 nM; (g) at least one polypeptide molecule corresponding to amino acid positions 122-134 of SEQ ID NO: 8 or a polymer thereof; (h) at least one polypeptide molecule of at least 13 amino acids and corresponding to a consecutive amino acid sequence within the range of amino acid positions 122-134 of SEQ ID NO: 8, the molecule binding to at least one HLA-DR molecule encoded by the alleles DRB1*1101, DRB1*1301 or DRB1*1501 with a binding activity <1000 nM; and (i) at least one pharmaceutically acceptable vehicle, wherein any polypeptide may contain at least one mutation such that the resultant mutant binds at least to one HLA-DR molecule encoded by the alleles DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701, DRB1*1101, DRB1*1301 or DRB1*1501 with a binding activity <1000 nM.